Site-specific targeting of antibody activity in vivo mediated by disease-associated proteases.

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Public Summary:
As a general strategy to selectively target antibody activity in vivo, a molecular architecture was designed to render binding activity dependent upon proteases in disease tissues. A protease-activated antibody (pro-antibody) targeting vascular cell adhesion molecule 1 (VCAM-1), a marker of atherosclerotic plaques, was constructed by tethering a binding site-masking peptide to the antibody via a matrix metalloprotease (MMP) susceptible linker. Pro-antibody activation in vitro by MMP-1 yielded a 200-fold increase in binding affinity and restored anti-VCAM-1 binding in tissue sections from ApoE$^{-/-}$ mice ex vivo. The pro-antibody was efficiently activated by native proteases in aorta tissue extracts from ApoE$^{-/-}$, but not from normal mice, and accumulated in aortic plaques in vivo with enhanced selectivity when compared to the unmodified antibody. Pro-antibody accumulation in aortic plaques was MMP-dependent, and significantly inhibited by a broad-spectrum MMP inhibitor. These results demonstrate that the activity of disease-associated proteases can be exploited to site-specifically target antibody activity in vivo.

Scientific Abstract:
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